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| 10/559,639 | 07/24/2006 | Dina Ben-Yehuda | 7640-X05-046 | 5095 |

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| EXAMINER | |
|---|---|
| STOICA, ELLY GERALD | |

| ART UNIT | PAPER NUMBER |
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| 1647 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/559,639 | BEN-YEHUDA ET AL. | |
| | Examiner | Art Unit | |
| | ELLY-GERALD STOICA | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *27-43* is/are pending in the application.

4a) Of the above claim(s) *35-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-34,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of group I (claims 27-34 and 42-43) and of the species Seq. Id. No. : 1 and 2 in the reply filed on 03/28/2008 is acknowledged. The traversal is on the ground that the peptides of the invention have pro-apoptotic properties as opposed to the species disclosed by Kasof et al. (The Journal of Biological Chemistry 276 (5):3238-3246 2001). This is not found persuasive because, as claimed in the first product claims, - 27-, the species are a naturally occurring cleavage product of the Livin polypeptide disclosed by Kasof et al. and therefore cannot form the basis for unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

### *Status of the claims*

2. Claims 27-43 are pending. Claims 35-41are withdrawn as being drawn to non-elected subject matter; claims 27-34 and 42-43 are being examined.

### *Claim Rejections - 35 USC § 101*

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27-29 rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. As claimed, the peptides are products of nature which will occur in the apoptosis processes.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 27, 28, 30-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the claims are drawn to a livin-derived peptide selected from one of p30-Livin α and p28- Livin β, wherein said p30-Livin α peptide comprises the sequence *substantially* as defined in SEQ ID NO:1, or functional analogues, derivatives or fragments thereof having pro-apoptotic activity, and wherein said p28- Livin β peptide comprises the sequence *substantially* as defined in SEQ ID NO :2, or functional *analogues*, *derivatives* or fragments thereof having pro-apoptotic activity and pharmaceutical compositions containing them. Thus, besides the specific peptides p30-Livin α and p28- Livin β which have adequate written description in terms that the

structure and the function is defined, the claims are drawn to a genus of peptides defined by functionality only.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, for the rest of the genus besides p30-Livin α and p28-Livin β (i.e. functional analogues, derivatives or fragments thereof) the only factor present in the claims is the functionality of the members of the genus. The specification provides, on pages 10-14, general guidance with respect to the terms functional analogues, derivatives or fragments thereof, that is, no specific guidance nor specific structures. There is no disclosed minimal structure needed to conserve the functionality of the peptides claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus but just for two members of the genus, p30-Livin α and p28- Livin β.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed functional analogues, derivatives or fragments and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the peptides p30-Livin α and p28- Livin β but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 27-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for p30-Livin α and p28- Livin β to induce apoptosis in certain cell lines, when triggered by certain apoptosis inducing regimens, does not reasonably provide enablement for functional analogues, derivatives or fragments of either p30-Livin α and p28- Livin β to induce pro-apoptotic activity, in all the cells and with any apoptotic trigger. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to livin-derived peptide selected from one of p30-Livin α and p28- Livin β, wherein said p30-Livin α peptide comprises the sequence substantially as defined in SEQ ID NO:1, or functional analogues, derivatives or fragments thereof having pro-apoptotic activity, and wherein said p28- Livin β peptide comprises the sequence substantially as defined in SEQ ID NO :2, or functional analogues, derivatives or fragments thereof having pro-apoptotic activity and pharmaceutical compositions containing them for inducing and or enhancing apoptosis. The apoptosis may be is induced by a treatment or agent selected from the group consisting of etoposide, anti-CD95/Fas, TNF-α and staurosporine and the cells may be malignant cells. The p30-Livin α peptide is denoted by the sequence as defined in SEQ ID NO:1 and p28- Livin β is denoted by the amino acid sequence as defined in SEQ ID NO :2.

The prior art recognizes the potential anti-apoptotic properties of Livin α and Livin β peptides and, in some cases even the pro-apoptotic properties of these peptides. However, there is a relatively narrow set of conditions in which the anti or pro apoptotic activity is observed. Absent a defined set of conditions for the experiments (i.e., particular cell lines and apoptotic triggers) the art is rather unpredictable because the apoptotic process *per se* is extremely complex and the intricate web of participating molecules is relatively unknown and thus very few predictions can be made *a priori*. For instance, no functional difference between Livin α and Livin β in regard to their ability to block Fas- and tumor necrosis factor(TNF)-receptor-induced apoptosis, upon their ectopic over expression in MCF 7 cells is noted. In contrast, differential anti apoptotic properties for the two isoforms have been described upon ectopic over expression in Jurkat cells: Livin α, but not Livin β, protected the cells from staurosporine-induced apoptosis, whereas apoptosis upon etoposide treatment was blocked only by the Livin β isoform (Crnković-Mertens et al., J. Mol. Med., 84, 232-240, 2006- p. 233, left col., first full paragraph). In HeLa cells, Livin β inhibition sensitized cells toward TNF α, an agent inducing the death-receptor pathway, and toward etoposide or UV irradiation, which are agents that induce the mitochondrial pathway. These events were linked to caspase-3 activation and PARP cleavage specifically upon inhibition of Livin β expression. In contrast, selective silencing of the Livin α isoform did not have any notable effect (Crnković-Mertens et al. p.239, left paragraph, lines 2-9). The differential anti apoptotic effect and even pro apoptotic effects are recognized by Ashhab et al. (FEBS Letters, 495, 56-60, 2001-cited by Applicant), which noted that, in Jurkat cells over expressing

Livin α or Livin β both block apoptosis induced by TNF-α and anti-CD95. On the other hand, Livin α but not β shows an intermediate anti apoptotic effect. Unexpectedly, Livin α was shown to have a slight pro-apoptotic effect when the cells were treated with etoposide, whereas Livin β was seen to have a strong protective effect. The specification discloses the sequences for just the p30-Livin α and p28- Livin β and no concrete direction for other functional analogues, derivatives or fragments thereof claimed. The cells in which the peptides can have an effect, disclosed in the working examples, are cells derived from melanoma, lymphoma, T-cell leukemia, epithelial cells, human embryonic kidney cells (like the 293 HEK cell line) or the 721.221 cell line. The apoptosis triggering agent disclosed are etoposide, anti-CD95/Fas, TNF-α and staurosporine.

Due to the large quantity of experimentation necessary to test the unspecified number of functional analogues, derivatives or fragments recited in the claims in all the cell types existent, by using all the apoptosis triggers known; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of peptides derived from inhibitors of apoptosis; and the breadth of the claims which fail to recite concrete structural limitations for the functional analogues, derivatives or fragments claimed, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in a manner commensurate with its full scope.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 27-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the independent claim 28 recites peptides that comprise functional analogues, derivatives or fragments of either the p30-Livin α and p28- Livin β peptides. Since the respective functional analogues, derivatives or fragments do not have an adequate written description, the metes and bounds of the claims could not be determined.

The term "substantially" in claim 28 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Also the metes and bounds of “functional analogues, derivatives or fragments of either the p30-Livin α and p28- Livin β peptides” cannot be determined since the terms are not adequately described.

It is also unclear how the intended use limitations of claims of claims 33-34 would further limit the claimed composition.

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 27-29 and 42-43 are rejected under 35 U.S.C. 102(a) as being anticipated by Nachmias et al. (Cancer Research, 63, 6340-6349, 10/01/2003).

Nachmias et al. teach that upon in the staurosporine induction of apoptosis in MeWo, a melanoma cell line that expresses high levels of Livin, a specific cleavage of both Livin isoforms, Livin α and Livin β ,in a time-dependent manner, fragments denominated as –p30-Livin α and p28 Livin - β were obtained (Fig.1a). Plasmid expression vectors containing DNA encoding p30-Livin α or p28- Livin β were transfected in 721.221 cells. Also taught is the use of viral vectors that containing the cDNA for Livin α or Livin β any desired to be expressed for viral infection of cells (p. 6341, left col. second heading) and, since the claim 43 recites a 'viral vector comprising DNA encoding" either p30-Livin α or p28-Livin β, the viral vectors containing DNA for Livin α and Livin β would also comprise the DNA encoding the claimed peptides. After triggering apoptosis by anti-CD95/Fas treatment, cells expressing p30-Livin α showed a much higher rate of apoptosis in comparison with wild-type 721.221 cells (Fig.5a), thus indicating that the cleavage of Livin not only eliminates its anti apoptotic activity but also produces a subunit with a marked pro-apoptotic effect. Transient transfection was used to assay for p30-Livin α and p28- β Livin functionality in 293T cells. A significantly higher

rate of apoptosis was obtained in the cells transfected with either p30-Livin α and p28-Livin β –in comparison with cells transfected with the full-length proteins or an empty vector (Fig.5c). The higher rate of apoptosis was noticed also in some primary culture melanoma cells correlated with the levels of p30-Livin α and p28- Livin β (p. 6345, left col. to p. 6346, right col., line 7; fig 6).

Thus claims 27-29 and 42-43 were anticipated by Nachmias et al.

***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nachmias et al. (Cancer Research, 63, 6340-6349, 10/01/2003).

The claims are drawn to a pharmaceutical composition comprising as active ingredient at least a livin-derived peptide selected from one of p30-Livin α and p28- Livin β, wherein said p30-Livin α peptide comprises the sequence substantially as defined in SEQ ID NO: 1, or functional analogues, derivatives or fragments thereof having pro-apoptotic activity, and wherein said p28- Livin β peptide comprises the sequence substantially as defined in SEQ ID NO :2, or functional analogues, derivatives or fragments thereof having pro-apoptotic activity. Also claimed is a viral vector comprising DNA encoding a p30-Livin α peptide as defined by SEQ ID NO: 1 or a p28-Livin β peptide as defined by SEQ ID NO:2.

The teachings of Nachmias et al. were presented supra. The reference also teach the results obtained in primary culture of melanoma cells which would prompt a person of ordinary skill in the art to consider treatment of malignant cells by inducing apoptosis using the p30-Livin α and p28- Livin β peptides (p. 6348). Even though Nachmias et al. do not expressly teach pharmaceutical compositions containing p30-Livin α and p28- Livin β peptides, the reference suggests the use of the polypeptides for treatment and that would inherently mean to have the peptides in a pharmaceutical

composition that could be delivered to patients. The level of skill in the art of pharmaceutical sciences was very high so that a person of ordinary skill in the art would be perfectly knowledgeable to formulate a pharmaceutical composition containing a peptide to a patient by multiple administration routes. Also, in the biological sciences, there would have been perfectly obvious to use a viral vector for delivery of a desired cDNA to a patient or a cell.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the core teachings of Nachmias et al. to design a pharmaceutical formulation with a reasonable expectation of success, due to the high skill in the art. The motivation to do so is offered by Nachmias et al, which suggests using the peptides for treatment of drug resistant malignant melanoma.

***Conclusion***

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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